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SECTION E

BIOLOGICAL WARFARE

Chapter 313

Biological Warfare and Bioterrorism

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Biological warfare, by treaty definition, is the use of "microbial . . . agents . . . for hostile purposes or in armed conflict." The treaty definition applies to states under international law; equally cogent is customary and intrastate law as it applies to groups and individuals, notably terrorists who pursue political aims, revenge, or other idiosyncratic agenda through the use of violence. During the Cold War, superpower states sustained major biological warfare technology programs, at least until 1975. Since then, the burden of concern has shifted to bioterrorism, either state sponsored or in the pursuit of fanatical aims of smaller groups.

Biological warfare has a long but sporadic history associated with the almost inevitable accompaniment of epidemic disease in military operations through the centuries. The possibly inadvertent accompaniment of smallpox and measles with the Conquistadors played a large part in the European conquest of the Western Hemisphere and likewise the Australian continent and Pacific Islands. However, recent episodes of the systematic use of microbial weapons have been rare—in contrast to the major involvement of their cousins, chemical weapons, in the trench warfare of World War I.

Since the advent of the Biological Warfare Convention, formally in force in 1975, the major task facing containment of biological warfare has been promulgation and enforcement of the Biological Warfare Convention—the most egregious recent challenge having come from Iraq. Saddam Hussein has not hesitated to use chemical weapons against Iran and against dissidents in Iraq and has often threatened to use biological warfare, but he never did even under the stresses of the Persian Gulf War (1990–1991). As governed the stalemate of the Cold War, an even larger framework of deterrence was operative. At this writing, the United Nations Special Commission is spasmodically investigating Iraq and seeking reassurance that its stockpiles and production facilities—notably of anthrax—had indeed been fully declared and demolished.

Today, as a result of deterrence, the principal threats of biological warfare are attributed to non-state actors, including state-sponsored terrorists and new breeds of sociopathic individuals and groups prepared to make war against society using motives that are hard to fathom. The scale of violence of such terrorist acts has escalated from demonstrative theater to the downing of jumbo aircraft and attacks on major buildings, as in Oklahoma City and New York City's World Trade Center. Had the World Trade Center collapsed, as was intended by the culprits, 100,000 citizens would have been at risk—an event on the scale of wartime Hiroshima or Nagasaki. Abroad, U.S. embassies have been targeted in Africa, with incidents thus far being limited to savage explosive attacks that have produced many civilian and bystander casualties.

The consideration of biological warfare has thus moved from the conventional military theater to a bioterrorism that puts millions of people in cities under the threat of artificially acquired infectious disease. Working in collaboration with every level of government and especially at the local and regional level, infectious disease specialists can play many instrumental roles:

1. Anticipation of threat agents and modalities of dissemination and their impact on public health
2. Assistance to local emergency authorities in planning for management of the consequences of a biological warfare attack
3. Participating in local public health teams in the epidemiologic investigation and definitive diagnosis of suspicious outbreaks
4. Acting as central agents in the medical and public health management of outbreaks and their further consequences for the life of the community
5. Assisting other branches of government in authentic assurance and guidance to the public to avert panic and chaos
6. Assisting when appropriate in taking measures to limit the further spread of contagious agents and to decontaminate affected facilities
7. Undertaking ongoing basic and translational research to sharpen the tools available for all these functions and further training of colleagues and supporting personnel
8. Instilling a globally shared ethos in condemnation of any possible use of biological warfare or offensive planning and preparation therefor
9. Maintaining networks of expertise that are available to public health and defense officials in confronting exotic agents for which such expertise is scarce and may be unavailable within government

The United States is on the verge of establishing a fully coordinated framework for responses on the part of government (President Bill Clinton's Presidential Decision Directive #62, May 22, 1998); as this framework is spelled out by further legislation and executive orders, infectious disease specialists in every major community will have no trouble locating where they can be of assistance.

ANTICIPATION OF THREAT AGENTS

Under conventional military doctrine, a biological warfare agent should be highly reliable, able to be targeted precisely at an enemy, cheap to produce, enjoy long shelf life and aerosol durability, and show limited epidemic spread. These criteria have converged to form a fairly short list of tier 1 agents (Table 313–1) that car be artificially aerosolized to deadly effect, regardless of their natural mode of transmission.

Most of these diseases are expected to follow a clinical course after biological warfare inoculation similar to that of the natural infections and to have limited capacity for person-to-person spread. (This objective cannot be ensured for the very large group subsumed

TABLE 313-1 Tier 1 Agents/Diseases

Anthrax
Plague
Tularemia
Brucellosis
Q fever
Alphaviruses
Venezuelan equine encephalitis
Western equine encephalitis
Eastern equine encephalitis
Viral hemorrhagic fevers
Smallpox—special category

under viral hemorrhagic fevers.) Empirical data are limited, but every expectation is that early antibiotic treatment will be effective against any of the bacterial culprits. (See other chapters for details.)

Aerosolized anthrax induces a disease quite distinct from the more usual and often survivable cutaneous variety. With intense involvement of mediastinal lymph nodes, it has a mortality approaching 100% if untreated before overt symptoms develop. Studies with primates suggest that early treatment with penicillin or doxycycline may be effective but may have to be prolonged for weeks and supplemented with vaccination or boostering. With heavy inocula, it is thought that some inhaled spores may remain dormant for long periods before germinating and becoming exposed to administered antibiotic.

No ex post facto specific treatment is known for the viral disorders, and for many of them there remain lacunae in our understanding of their natural history.

In a military defense setting, physical protection (masks and suits) plays the largest role—the same defense as against chemical weapons. In addition, mass prophylactic vaccination (e.g., against anthrax and some viral agents) is feasible in principle and has been adopted as routine for the U.S. Armed Forces. Likewise, routine monitoring of suspected clouds in the theater of operations should be conducted to provide early warning of chemical and biological warfare threats.

The changing threat, with special apprehension about vengeful individuals, forces our attention to agents and media beyond those of tactical military consequence. We can hardly monitor every civil airspace, although special attention has been paid to spectacular sites and events such as the Olympics—recalling the attacks at Munich in 1972. Massive outbreaks of foodborne and waterborne disease remind us of these vehicles for intentional infection. Other consumer product tampering has occurred on a minor scale for homicidal purposes; such tampering might be escalated manyfold for harassment of a corporation or a nation. Toxic tampering of a few grapes led to great economic losses for Chile in 1989. Similar harassment against domestic products, farm animals, or crops might be motivated for crass gains in the futures markets. Some terrorist mentalities may be undeterred by the untold havoc that would ensue from the reintroduction of smallpox into a global herd, the younger half of which is by now unvaccinated.[1] Smallpox had been discounted as a "rational" weapon because its spread might be uncontrollable. Now, our policy dilemmas about the merits (and hazards) of reintroducing vaccination are compounded by the technical ones of rediscovering and authenticating reliable seed stock and reconstituting the capacity for production of vaccine.

All things considered, anthrax has long held pride of place as an agent fairly easily grown and whose spores have long-lasting durability. Efficient dissemination is another matter: to produce a cloud of 1- to 5-μm particles takes more than a garden sprayer, and its action is subject to many vagaries of wind, rain, sunshine, and atmospheric turbulence. The oft-quoted figures of a potential for 10,000 casualties per kilogram of spore suspension are within the envelope of possibility, but as an optimal case combining substantial technical expertise, including meteorologic insight. The requisite technology remains within the reach of any determined state and requires investments in the low millions of dollars. That the reliability of outcome probably remains low may be less consequential to a clandestine terrorist, who can always try again, than to a military planner in a moment of tactical crisis. State-sponsored terrorism remains the most strident threat, and we should be particularly alert in connection with military confrontations with the states (mainly in the Middle East) that have had a history of use of such instrumentalities. Even if the principal state actors remain influenced by our deterrence strategies, others are often eager to precipitate hostilities in furtherance of their domestic political conflicts. The looming nuclear arms race on the Indian subcontinent also raises new alarms that these and other parties will look to biological warfare as a means of influencing the strategic balance there.

PLANNING FOR CONSEQUENCE MANAGEMENT

Absent a major catastrophic incident, it has been difficult to mobilize much attention to prior planning for a biological warfare attack. That nonchalance was strained by the Aum Shinrikyo nerve gas attack (1995) on the Tokyo subway system and by subsequent revelations that the cult had also stockpiled many agents and had attempted to deploy anthrax. New York City and metropolitan Washington, D.C., have taken the lead to organize themselves locally, with modest assistance from federal agencies and funding under the Nunn-Lugar-Domenici legislation (1996). In many cities, as in New York, fire departments also have emergency medical service and hazardous material release responsibilities. Their principals have rightly expressed concern for the welfare of the first responders, who play a vital role in situational assessment and in damage limitation and rescue services. Without special training and equipment, they could readily be booby-trapped and remain oblivious to an infectious presence for hours and days until symptoms develop, whereupon it may be too late for effective intervention. Coordination with law enforcement—the police department locally, the FBI with jurisdiction for criminal terrorism and eager to apprehend culprits and collect and preserve evidence—must also be planned and exercised in advance. Then, health providers must be mobilized for diagnosis, triage, emergency medical treatment, and disposition for further follow-up, in settings likely to strain all available hospital capacities. Professionals must also be responsible for certifying decontamination and for signaling all clear or ongoing vigilance to the public.

Infectious disease experts will play an indispensable role in motivating sober attention to these contingencies and in assisting at every stage of the planning for mitigation. They must weigh the risks and benefits of arousing public attention, but not hysteria. Attention must always be paid to the risk that every constructive step, when publicly displayed, may also inspire a culprit to circumvent the progress made. It would be well to not publicize technical details of methods of cultivation of prospective agents or their effective dissemination. Microaerosol generating equipment may also have to be put under special license, much as the distribution of cultures of special pathogens is now subject to Public Health Service registration in the United States.

EPIDEMIOLOGIC INVESTIGATION AND DEFINITIVE DIAGNOSIS

Terrorist theater (which includes hoaxes) apart, serious malefactors are unlikely to give advance, specific warning. Any major explosion may be contaminated with "bioshrapnel" to complicate the tasks of salvage and rescue, a caution that the first responders have begun to internalize. However, the first indicator of a major outbreak may well be a cluster of symptomatic or soon moribund cases. Isolated fatalities from undiagnosed febrile illness are not so uncommon, especially among immunocompromised individuals, who could be the most sensitive indicators. Special efforts must be applied to collect statistics, on a day-to-day basis, that might be evidence of suspected clustering and attract particularly energetic efforts at prompt diagnosis. The event might be an outbreak of natural viral disease, perhaps an import. So even a laboratory or pathologic diagnosis may not at first reveal man-made versus natural provenance. (If it is pulmonic anthrax, there would be little doubt.) In either event, prompt epidemiologic inquiry is indispensable to define the bounds of the outbreak in order to identify the most effective interventions to save others not yet symptomatic. The hope is that the earliest cases might reflect the persons most heavily dosed. They may be beyond saving, but the bulk of the exposed population would have longer incubation periods and could be reached for, say, antibiotic treatment. Effective consequence management relies on epidemiologic modeling of the outbreak and calls on meteorologic as well as infectious disease insights. Moreover, all this must be done within hours!

Waterborne outbreaks, in principle, have similar features—and the added imperative to shut down continued sources of infection. Emergency disinfection of water is easiest—by boiling; how that would apply to anthrax spores has probably not been studied. The bioterror threat is just one additional argument for more diligent monitoring of municipal water supplies, not just at the treatment plant (if any) but at major terminal distribution points as well.

Food and other media could be more widespread, especially in light of the relentless international commerce—consider the *Cyclospora* outbreak eventually traced to Guatemalan raspberries. In 1995, more than 200,000 Americans were infected with *Salmonella enteritidis* from ice cream connected with a premix contaminated with unpasteurized egg yolks. This national outbreak was presumably unintentional. Another local one in 1984 in Oregon affected 751 people; this outbreak was traced to malicious inoculation of salad bars and was intended to influence a local election.

Definitive diagnosis may require special skills and reagents, for which the ultimate resort may be the Centers for Disease Control and Prevention in Atlanta or the U.S. Army Research Institute for Infectious Diseases located at Fort Detrick, Maryland. Local preparedness will be enhanced either by pre-established confidence of communication with these centers or by the qualification of a local infectious disease laboratory and an alert to invoke these resources at a reasonably early stage.

MEDICAL AND PUBLIC HEALTH MANAGEMENT OF OUTBREAKS

Establishment of the diagnosis and epidemiologic model, as best as possible from the available data, opens the way for active management. We have no historical precedent to draw on; the nearest analogue would be natural disasters such as earthquakes and hurricanes. The additional opportunity, as well as burden, is the utility of prompt, well-targeted interventions if instituted within hours. With the likelihood of limited resources of time and medicinals, some form of triage is inevitable to focus these resources on persons who will achieve the most benefit. The worried (and angry and resentful) well are likely to greatly outnumber those needful of treatment—and that criterion may be difficult to authenticate at the earliest and hence most treatable stages. As with other emergencies, a host of practical problems from record keeping to who will pay the bills will also confound optimal treatment. Interim facilities outside of hospitals will need to be established and staffed. Little wonder that there is a universal expectation of calling in federal resources—Public Health Service, specialized Marine Corps units—but at best these resources will take time to mobilize and transport and themselves have limited further scope. Plans have been initiated for training National Guard units in several states to provide for rapidly mobilizable, but local reserves.

One of the immediate issues is the choice and availability of antibiotics. Given the possibility of drug-resistant pathogens, a cocktail might be prescribed—but such a combination may face poorly understood details of drug interactions and enhance the possibility of adverse side effects. Detailed, advance planning should be implemented to locate stockpiles of antibiotics, most effectively planned boluses in the normal distribution pipeline, and make arrangements for their transport, safeguarding, and orderly distribution. Even so, shortages are inevitable, and difficult decisions may be in the offing about stretching out the doses, mixing drugs, and whether to use material aged beyond the nominal expiration date.

This kind of planning is still at a developmental stage, and it is obvious that infectious disease experts need to be at the center from planning through execution.

ASSURANCE AND GUIDANCE TO THE PUBLIC IN AVERTING PANIC AND CHAOS

The media will not be silent during such episodes, and their far-flung intelligence could be invaluable in assembling important information. They will be disseminating what they learn or surmise to wide audiences, near and far. It would be most helpful if they can get that information from well-informed professionals and best if they could speak with a consistent voice in collaboration with operating governmental officials about the implications of an outbreak and the measures entailed for citizens. The same applies to the precautionary planning and exercises that are being mounted in major cities.

Caregivers may need special attention: their services are crucial and they must be sustained, and they may be at the brunt of hazardous exposure and psychic trauma from caring for the victims. The disposition of remains will be a further stress, materially and psychically.

Meanwhile, there will be no holiday for other civic functions, including health providers for other ailments, not to mention the personal, social, and economic life of the city—all functions that need to be restored promptly.

LIMITING THE FURTHER SPREAD OF CONTAGIOUS AGENTS

From a public health perspective, high priority must be given to the decision about the hazards of spreading infection further and, if it does spread, what can be done to persuade victims to limit their movements. In any event, those potentially exposed need advice and resources about initial and follow-up treatment and whether it can be acquired away from the initial treatment sites. Other implications of mass out-migration—and whether or how to avert it—leap to mind. Nor can it be assumed that the first attack will be the last one or at the same site.

Although the greatest hazards derive from the primary aerosol, spores residual on interior surfaces or vehicles or in heavily trafficked areas have some small chance of reaerosolization and continued threat. Exposed food and water supplies will need special validation. Decontamination protocols will have to be reassessed for the local contingency and some measure of laboratory verification invoked for the safe use of such sites.

ONGOING BASIC AND TRANSLATIONAL RESEARCH

Innumerable challenges to skilled judgment have already been posed throughout this discussion. They call for additional translational research to sharpen the tools available for all these functions: optimum treatment modalities for exotic diseases and assessment of the compromises necessitated by the exigencies of a crisis. In addition, infectious disease specialists by the very nature of their work are deeply involved in the underlying research on pathogenesis, immunity, and treatment. We are particularly frustrated in the treatment of viral infections, which cries out for further discovery in small-molecule antivirals, in interventions in pathogenetic mechanisms, in the acceleration of active immunity, and in the possible use of preformed antibodies.

Unhappily, the same biotechnological science that can lead to therapeutic advances can be diverted to making further mischief with genetically engineered constructs. Published work from Russia already points to the prospects of augmenting the virulence and offering vaccine escape for anthrax by importing toxins from other species.[2] Such research, if continued—and it may have to be to enable defenses to be contrived—must be carefully regulated and utterly transparent to provide some reassurance about its purposes.

All these research programs also entail further specialized training of colleagues and supporting personnel.

GLOBALLY SHARED ETHOS IN CONDEMNATION OF BIOLOGICAL WARFARE

The infectious disease worker knows better than anyone else how hard we have to work to keep up with natural disease outbreaks.

The contemplation of malicious compounding of nature's hazards is almost unbearable. The infectious disease community is also aware of the indivisible hazards to all humanity if biological warfare were to be routinized in the realm of human conflict. Technically, defense against biological warfare is already speculative; the recipes in this article are for damage mitigation, and the net of the most effective defense of a city may still be the death of thousands of victims. This awareness may alert professionals to the need to build a network of resolve that cuts across national boundaries to forfend the thought of biological warfare. They can exert their influence to reinforce that moral resolve with the consolidation of national policies and the institutionalization of international law. The same professionals may first need to enhance their own familiarity with these issues. This distasteful necessity is immediately derived from infectious disease specialists' unique understanding of the relentless competition between the human and micropredatory species.

REFERENCES

1. Breman JG, Henderson DA. Poxvirus dilemmas—monkeypox, smallpox, and biological terrorism. N Engl J Med. 1998;339:556–557.
2. Pomerantsev AP, Staritsin NA, Mockov YV, et al. Expression of cereolysine AB genes in *Bacillus anthracis* vaccine strain ensures protection against experimental hemolytic anthrax infection. Vaccine. 1997;15:1846–1850.

BIBLIOGRAPHY

Ali J, Rodrigues L, Moodie M. Chemical-Biological Defense Handbook. Alexandria, Va: Jane's Information Group; 1997.

Carus WS. Bioterrorism and Biocrimes: The Illicit Use of Biological Agents in the 20th Century. Washington, DC: Center for Counterproliferation Research, National Defense University; 1998.

Falkenrath RA, Newman RD, Thayer BA. America's Achilles' Heel: Nuclear, Biological, and Chemical Terrorism and Covert Attack. (BCSIA Studies in International Security). Cambridge, Mass: MIT; 1998.

Lederberg J, ed. Biological Weapons: Limiting the Threat (BCSIA Studies in International Security). Cambridge, Mass: MIT; 1999.

Office of Technology Assessment. Proliferation of weapons of mass destruction: Assessing the risks. Publication No. OTA-ISC-559. Washington, DC: US Government Printing Office; August 1993.

Office of Technology Assessment. Technologies Underlying Weapons of Mass Destruction. Publication No. OTA-BP-ISC-115. Washington, DC: US Government Printing Office; December 1993.

Poupard JA, Miller LA. Biological warfare. In: Lederberg J, ed. Encyclopedia of Microbiology, v. 1. San Diego: Academic Press; 1992:297–308.

Sidell FR, Takafuji ET, Franz DR, eds. Medical Aspects of Chemical and Biological Warfare. Washington, DC: Office of the Surgeon General; 1997.

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